The New England Journal of Medicine

VOLUME 337 NOVEMBER 6, 1997 NUMBER 19

A COMPARISON OF RECOMBINANT HIRUDIN WITH A LOW-MOLECULAR-WEIGHT HEPARIN TO PREVENT THROMBOEMBOLIC COMPLICATIONS AFTER TOTAL HIP REPLACEMENT

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ABSTRACT

Background Patients who undergo total hip replacement have a high risk of thromboembolic complications. Recombinant hirudin (desirudin), a specific inhibitor of thrombin, represents a new development in antithrombotic therapy. We compared the efficacy and safety of desirudin with those of a low-molecular-weight heparin (enoxaparin) for the prevention of thromboembolic complications in patients undergoing primary total hip replacement.

Methods Both treatments, which were assigned in a randomized, double-blind manner, were started preoperatively: enoxaparin on the evening before surgery, and desirudin within 30 minutes before the start of surgery. The dose of desirudin was 15 mg subcutaneously twice daily, and the dose of enoxaparin was 40 mg subcutaneously once daily. The duration of treatment was 8 to 12 days. Deep-vein thrombosis was verified by bilateral venography performed at the end of the treatment period or earlier, if there were clinical signs of deep-vein thrombosis.

Results At 31 centers in 10 European countries, 2079 eligible patients were randomly assigned to receive desirudin or enoxaparin. A total of 1587 patients were included in the primary analysis of efficacy. In the desirudin group, as compared with the enoxaparin group, there was a significantly lower rate of proximal deep-vein thrombosis (4.5 vs. 7.5 percent, $P=0.01$; relative reduction in risk, 40.3 percent) and a lower overall rate of deep-vein thrombosis (18.4 vs. 25.5 percent, $P=0.001$; relative reduction in risk, 28.0 percent). The safety profiles were similar in the two treatment groups.

Conclusions When administered 30 minutes before total hip replacement, desirudin is more effective than enoxaparin in preventing deep-vein thrombosis. (N Engl J Med 1997;337:1329-35.)

DEEP-VEIN thrombosis is a common complication of total hip replacement, and a variety of methods to prevent it have been studied. The rationale for the use of a specific thrombin inhibitor such as recombinant hirudin (desirudin) stems from its direct inactivation of both free and fibrin-bound thrombin; it requires no plasma cofactors in the inhibition of thrombus growth.[1-3] Desirudin differs from natural hirudin in the absence of a sulfate group.

In two multicenter studies, desirudin (at a dosage of 15 mg twice daily) has been found to be safe and superior to unfractionated heparin (5000 IU three times daily) in the prevention of deep-vein thrombosis after total hip replacement.[4,5] Low-molecular-weight heparin preparations are perceived to be more efficacious than unfractionated heparin in patients who have undergone orthopedic surgery.[6-8] We therefore used low-molecular-weight heparin as a comparison drug and evaluated the antithrombotic efficacy and safety of desirudin as compared with those of a standard regimen of enoxaparin in patients undergoing total hip replacement.

METHODS

Patients

Consecutive patients 18 years of age or older, weighing 50 kg or more, who were scheduled to undergo elective primary total

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hip replacement were eligible. The most important criteria for exclusion were childbearing potential; previous inclusion in the trial; bilateral hip operation; hip surgery or fracture of the leg within the previous three months; other major surgery within the past month; hemostatic or bleeding disorders; a history of hemorrhagic stroke, intracranial or intraocular bleeding, or cerebral ischemic attacks within the past six months; gastrointestinal or pulmonary bleeding within the past three months; uncontrolled hypertension; renal impairment, nephrectomy, or kidney transplantation; and known allergy to hirudin, heparin, or contrast medium.

Study Design

The study was a multicenter, randomized, double-blind trial. The revised Declaration of Helsinki and the Guidelines for Good Clinical Practice were followed.[9] The study was approved by an ethics review board at each center. Written informed consent was obtained from each patient before his or her enrollment in the trial. An independent safety committee monitored reported adverse events, bleeding complications, laboratory abnormalities, and episodes of deep-vein thrombosis as assessed locally.

Treatment Regimens and Trial Drugs

Desirudin (Revasc; CGP 39393), a 65-amino-acid polypeptide with a molecular weight of 6964 and about 12,000 thrombin-inhibiting units per milligram of protein, was produced by recombinant DNA technology in yeast (*Saccharomyces cerevisiae*) and supplied by Novartis (Ciba–Geigy; Basel, Switzerland). It was produced and purified in collaboration with GEN Therapeutica Vertriebs, Bad Zwischenahn, Germany. Enoxaparin, a low-molecular-weight heparin, was manufactured by Rhône–Poulenc Rorer, Maison Alfort, France. Desirudin was administered in two doses of 15 mg each per day, and enoxaparin in a dose of 40 mg once a day. The first injection of desirudin was given within 30 minutes before the start of surgery, but after the induction of regional-block anesthesia, if that was used. The first injection of enoxaparin was given on the evening before surgery. Both drugs were administered by subcutaneous injection during a planned period of 8 to 12 days. Placebo injections were given to complete the double-blind design. The regimens of the study drugs followed the recommendations of the manufacturers.

The use of other drugs known to have effects on vascular integrity, fibrinolysis, coagulation, or platelet function was prohibited for one week before surgery and during the study treatment, with the exception of nonsteroidal antiinflammatory agents with short half-lives and aspirin at a dose of less than 325 mg per day. In the event of bleeding, appropriate blood products and plasma expanders were recommended. Venography was mandatory after the cessation of the study drug. After discontinuation of the study drug, the patients were allowed to continue other regimens for prevention, at the discretion of each center.

Thromboembolic Events

The primary variable with respect to efficacy was the number of confirmed major thromboembolic events during the treatment period, defined as proximal deep-vein thrombosis, fatal or nonfatal pulmonary embolism, or unexplained death. Mandatory bilateral ascending venography was performed at the end of the treatment period or earlier, if clinical symptoms occurred. Pulmonary embolism had to be confirmed by ventilation–perfusion scanning indicating a high probability of the diagnosis or by pulmonary angiography.[10] In cases of death, an autopsy specifically aimed at the detection of thromboembolism was performed whenever possible. In cases of unexplained death without autopsy, the outcome was considered to have been a thromboembolic event.

Bilateral venography was performed by the Rabinov and Paulin technique, with minor modifications.[11-13] Tourniquets were avoided in order to facilitate filling of all the deep veins and to improve differentiation between intraluminal clots and areas of insufficient filling or variable flow defects. A standard volume of at least 100 ml of nonionic, low-osmolality contrast medium (240 to 300 mg of iodine per milliliter) was injected into each leg. Each of the three vein segments in the proximal region were examined in at least two projections, and the calf in three different views. The minimal mandatory examination comprised nine images of each leg. All images were documented on long films. All deep stem veins, including the muscular veins of the calf, had to be adequately opacified up to the inferior caval vein. Visualization of the deep femoral and internal iliac veins was, however, not mandatory (veins could not be visualized for anatomical reasons in some patients). All venograms were assessed in a central radiology department by consensus of two radiologists who were unaware of the results recorded at the local centers. The only criterion for deep-vein thrombosis was the presence of a constant intraluminal filling defect of unvaried shape on at least two images. On the basis of the venograms, each vein was classified as normal, as having deep-vein thrombosis, or as unable to be assessed. The venogram was defined as inadequate for assessment if only one leg was examined or if any of the deep stem veins were inadequately visualized and no thrombus could be found — that is, if the absence of deep-vein thrombosis could not be verified. Deep-vein thrombosis above or in a popliteal vein was defined as proximal deep-vein thrombosis.

Safety

Perioperative blood loss was defined as bleeding recorded up to 12 hours after the start of surgery, and postoperative blood loss as that recorded from 12 hours after the start of surgery up to postoperative day 6. Transfusion with whole blood, concentrates of red cells, and plasma expanders was recorded. The main outcome variable with respect to safety was bleeding complications, defined as blood loss, serious bleeding episodes, and wound infection, dehiscence, or hematoma. Serious bleeding episodes were defined as a need for the perioperative transfusion of more than five units of whole blood or concentrates of red cells; a need for the transfusion of seven units at any time after the start of surgery; or total blood loss of more than 3500 ml. Any adverse events during prophylaxis were recorded. During six weeks of follow-up, all clinical thromboembolic events in randomized patients were recorded.

Statistical Analysis

The planned size of the sample for this study was 1000 patients in each treatment group. This number was based on an expected incidence of 6.5 percent for major thromboembolic events in patients treated with enoxaparin and an absolute difference of at least 3.25 percent between the rates in the two groups, with an overall significance level of 5 percent and a power of 80 percent, taking into account an estimated 25 percent dropout rate.[14] The primary outcome was analyzed by logistic regression with the treatment group and the country as fixed factors. The analysis included all the patients who could be evaluated — that is, all patients who had an adequate venogram, confirmed pulmonary embolism, or unexplained death, except for patients treated concomitantly with dextran or anticoagulants. Patients with an inadequate venogram were excluded from the analysis of efficacy because the absence of deep-vein thrombosis could not be confirmed. The influence of confounding factors on the incidence of deep-vein thrombosis was evaluated by logistic-regression analysis. All randomized patients were included in the evaluation of safety, which incorporated data on blood loss, transfusion requirements, bleeding complications, and adverse events.

RESULTS

Of the 4831 consecutive patients screened for eligibility between April 1994 and November 1995, 2752 patients were excluded before randomization,

mainly for administrative reasons or because they did not give informed consent. At 31 participating centers in 10 European countries, 2079 patients were randomly assigned to treatment groups.

A total of 2051 of these 2079 patients underwent surgery. There were no significant differences in the distribution of demographic characteristics, types of surgery or anesthesia, or risk factors between the two study groups (Table 1). The mean (±SD) duration of treatment was 9.7±1.1 days in the enoxaparin group and 9.8±1.1 days in the desirudin group, and 97 percent of the patients in each treatment group received prophylaxis for at least 9 days.

A total of 785 patients in the enoxaparin group and 802 in the desirudin group for whom data on outcomes could be evaluated were included in the primary analysis of efficacy (Table 2). The main reason for exclusion from the efficacy analysis was that venography was not performed or that it was deemed inadequate on central assessment. Major violations of the protocol were few, and there were no significant differences in their frequency between the treatment groups (Table 2).

The rates of thromboembolic events are summarized in Table 3. In the primary analysis of efficacy, a total of 99 patients (6.2 percent) had a major thromboembolic event (proximal deep-vein thrombosis, pulmonary embolism, or unexplained death): 39 of 802 (4.9 percent) in the desirudin group and 60 of 785 (7.6 percent) in the enoxaparin group ($P=0.02$), a relative reduction in risk of 36.4 percent (95 percent confidence interval, 5.9 to 57.0 percent). There was a significant reduction in the incidence of proximal deep-vein thrombosis in the desirudin group (36 of 802 [4.5 percent]) as compared with the enoxaparin group (59 of 785 [7.5 percent], $P=0.01$) — a relative reduction in risk of 40.3 percent (95 percent confidence interval, 10.7 to 60.1 percent). In addition, there was a significant reduction in the overall rate of deep-vein thrombosis in the desirudin group (142 of 773 [18.4 percent]) as compared with the enoxaparin group (196 of 768 [25.5 percent], $P=0.001$) — a relative reduction in risk of 28.0 percent (95 percent confidence interval, 12.8 to 40.6 percent).

Pulmonary embolism was confirmed, according to prespecified criteria, in two patients in each treatment group. One of the patients in the enoxaparin group had confirmed proximal deep-vein thrombosis in addition to pulmonary embolism. One patient in the desirudin group had cardiac arrest during surgery and died. This case was included as a major thromboembolic event, since no autopsy was performed and thus embolism could not be ruled out. This was the only case classified as unexplained death. In the enoxaparin group, one patient died of a myocardial infarction on the first postoperative day and was therefore excluded from the efficacy analysis.

TABLE 1. BASE-LINE DEMOGRAPHIC CHARACTERISTICS AND RISK FACTORS IN THE TWO STUDY GROUPS.

VARIABLE	ENOXAPARIN GROUP	DESIRUDIN GROUP
No. randomized	1036	1043
No. undergoing surgery	1023	1028
Age — yr		
Median	67	66
Range	18–87	27–90
Weight — kg		
Median	74	73
Range	43–128	42–120
Obesity — no. (%)*	431 (41.6)	428 (41.0)
Female sex — no. (%)	622 (60.0)	590 (56.6)
Previous thromboembolism — no. (%)	62 (6.0)	68 (6.5)
History of cancer — no. (%)	128 (12.4)	128 (12.3)
Primary diagnosis — no. (%)		
Osteoarthritis	994 (95.9)	1002 (96.1)
Rheumatoid arthritis	11 (1.1)	8 (0.8)
Osteonecrosis	17 (1.6)	17 (1.6)
Miscellaneous	14 (1.4)	16 (1.5)
Characteristics of surgery		
Regional anesthesia — no. (%)	571 (55.8)	573 (55.7)
Cemented prosthesis — no. (%)	453 (44.3)	459 (44.6)
Non-cemented prosthesis — no. (%)	397 (38.8)	402 (39.1)
Hybrid prosthesis — no. (%)	173 (16.9)	167 (16.2)
Duration of operation — min		
Median	80.0	82.0
Range	25–345	22–297
Therapy with nonsteroidal antiinflammatory agent or aspirin — no. (%)	705 (68.1)	722 (69.2)
Cigarette smoker — no. (%)	186 (18.0)	157 (15.1)

*Obesity was defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 27.2 for men and more than 26.9 for women.

TABLE 2. PATIENTS INCLUDED IN THE ANALYSIS AND REASONS FOR EXCLUSION.*

VARIABLE	ENOXAPARIN GROUP	DESIRUDIN GROUP
Randomized — no.	1036	1043
Underwent surgery — no. (%)	1023 (98.7)	1028 (98.6)
Able to be evaluated — no. (%)		
Primary-outcome analysis	785 (75.8)	802 (76.9)
Secondary-outcome analysis	768 (74.1)	773 (74.1)
Excluded from primary-outcome analysis — no. (%)	251 (24.2)	241 (23.1)
Reason for exclusion — no. (%)		
Operation canceled	13 (1.3)	15 (1.4)
Venography not performed	119 (11.5)	101 (9.7)
Venograms inadequate	102 (9.8)	109 (10.5)
Major protocol violation	17 (1.6)	16 (1.5)
Left study prematurely — no. (%)	61 (5.9)	70 (6.7)

*The patients included in the analysis of primary outcomes were those with adequate venograms verifying the presence or absence of proximal deep-vein thrombosis, those with fatal or nonfatal pulmonary embolism, and those with unexplained death. The analysis of secondary outcomes also included those with distal deep-vein thrombosis.

TABLE 3. THROMBOEMBOLIC EVENTS.*

EVENT	ENOXAPARIN GROUP†	DESIRUDIN GROUP	P VALUE	REDUCTION IN RELATIVE RISK (95% CI)
	no. (%)			%
Deep-vein thrombosis				
Proximal	59 (7.5)‡	36 (4.5)§	0.01	40.3 (10.7–60.1)
Overall	196 (25.5)¶	142 (18.4)‖	0.001	28.0 (12.8–40.6)
Pulmonary embolism	2 (0.3)	2 (0.2)	—	—
Unexplained death	0	1 (0.1)	—	—

*In the enoxaparin group, 785 patients could be evaluated for the primary outcome, and 768 for the secondary outcome. In the desirudin group, the respective numbers were 802 and 773. CI denotes confidence interval.

†One patient in this group had both proximal deep-vein thrombosis and pulmonary embolism.

‡The 95 percent confidence interval for the incidence is 5.8 to 9.6 percent.

§The 95 percent confidence interval for the incidence is 3.2 to 6.2 percent.

¶The 95 percent confidence interval for the incidence is 22.5 to 28.8 percent.

‖The 95 percent confidence interval for the incidence is 15.7 to 21.3 percent.

Analysis of the location of deep-vein thrombosis showed that thrombi occurred predominantly in the leg in which hip replacement had been performed, although in a substantial proportion of patients thrombi were located in the contralateral leg or in both legs (Table 4). Many patients had multifocal thrombi, and bilateral thrombi were more frequent in the enoxaparin group (Table 4).

The influence of age, sex, the type of anesthesia, the type of prosthesis, and the presence or absence of obesity was evaluated in a logistic-regression model. Age ($P<0.001$), type of anesthesia (general vs. regional; $P<0.001$), presence or absence of obesity ($P<0.01$), and type of prosthesis (cemented vs. noncemented; $P<0.02$) had a significant influence on the risk of deep-vein thrombosis. The significant effect of treatment persisted, however, after adjustment for these prognostic factors. The rates of deep-vein thrombosis varied among the different countries, from 2.2 percent to 10.7 percent for proximal deep-vein thrombosis and from 10.5 percent to 33.3 percent for deep-vein thrombosis overall. There was no interaction between treatment and country.

During the treatment period, symptoms of deep-vein thrombosis were noted in 23 patients (1.1 percent), 11 receiving enoxaparin and 12 receiving desirudin. The diagnosis was confirmed by venography in four patients in the enoxaparin group and two in the desirudin group. Pulmonary embolism was suspected on clinical grounds in four patients in the enoxaparin group and eight in the desirudin group. The diagnosis was confirmed by means of ventilation–perfusion scanning in two patients in each group.

During the follow-up period, deep-vein thrombosis was suspected on clinical grounds in 21 patients (1.0 percent) and symptoms of pulmonary embolism in 11 patients (0.5 percent). The diagnosis of deep-vein thrombosis was confirmed in three patients in the enoxaparin group and six patients in the desirudin group. Five patients had verified pulmonary embolism, four in the enoxaparin group and one in the desirudin group. During the follow-up period, four patients died — one in the enoxaparin group and three in the desirudin group. The reasons for death were cardiac failure in the patient in the enoxaparin group and pulmonary embolism, cardiac failure, and cerebral hematoma in one patient each in the desirudin group. These late events were not included in the analysis of efficacy.

All 2079 patients who received trial medication were included in the overall evaluation of the safety and tolerability of the drugs. A total of 2051 patients underwent surgery and could be included in the analysis of blood loss and transfusion requirements (Table 5). The median perioperative blood loss was 950 ml in both groups; total blood loss was

TABLE 4. LOCATION OF DEEP-VEIN THROMBI.*

LOCATION	ENOXAPARIN GROUP		DESIRUDIN GROUP	
	PROXIMAL (N=784)	OVERALL (N=767)	PROXIMAL (N=799)	OVERALL (N=770)
	number (percent)			
Leg undergoing surgery	52 (6.6)	122 (15.9)	34 (4.3)	85 (11.0)
Contralateral leg	3 (0.4)	31 (4.0)	1 (0.1)	37 (4.8)
Both legs	4 (0.5)	43 (5.6)	1 (0.1)	20 (2.6)

*Only patients who could be evaluated and who had adequate venograms are included. Many patients had multifocal thrombi. Bilateral thrombi were significantly more frequent in the enoxaparin group ($P=0.003$).

1200 ml in the enoxaparin group and 1240 ml in the desirudin group. There were no significant differences between the two groups with respect to perioperative, postoperative, or total blood loss. The number of patients who received transfusions and the amount of blood products transfused, as well as the use of plasma expanders, were similar in the two treatment groups. The rates of serious bleeding episodes, wound hematoma, wound dehiscence, and deep infections were essentially equal in the two groups (Table 5). There were no cases of thrombocytopenia. The safety committee did not suggest any modifications of the trial at any time.

TABLE 5. BLOOD LOSS, TRANSFUSION REQUIREMENTS, AND COMPLICATIONS RELATED TO BLEEDING IN PATIENTS WHO UNDERWENT SURGERY.

VARIABLE	ENOXAPARIN GROUP (N=1023)	DESIRUDIN GROUP (N=1028)
Blood loss — ml		
Perioperative		
Median	950	950
Range	80–5000	110–6800
Postoperative		
Median	200	250
Range	0–2400	0–1460
Total		
Median	1200	1240
Range	220–5710	120–6800
Transfusions		
Red-cell concentrate		
Patients with transfusions — no. (%)	534 (52.2)	524 (51.0)
Volume — ml		
Median	600	600
Range	200–4200	200–4200
Whole blood		
Patients with transfusions — no. (%)	214 (20.9)	226 (22.0)
Volume — ml		
Median	800	675
Range	100–3000	100–2210
Plasma expanders		
Patients with transfusions — no. (%)	787 (76.9)	786 (76.5)
Volume — ml		
Median	1000	1000
Range	50–4500	100–3125
Complications — no. (%)		
Serious bleeding*	20 (2.0)	20 (1.9)
Wound dehiscence	5 (0.5)	6 (0.6)
Deep wound infections	2 (0.2)	2 (0.2)
Wound hematoma	81 (7.9)	85 (8.3)
Injection-site hematoma	6 (0.6)	29 (2.8)

*Serious bleeding was defined as any of the following: perioperative transfusion of more than five units of whole blood, red-cell concentrate, or both; transfusion of more than seven units of whole blood, red-cell concentrate, or both, at any time; or transfusion of a total of more than 3500 ml of blood.

DISCUSSION

In this study, we compared a thrombin inhibitor, desirudin, with a low-molecular-weight heparin, enoxaparin, in patients undergoing total hip replacement. We found that the efficacy of desirudin was superior to that of enoxaparin. There was a significantly lower rate of proximal deep-vein thrombosis in the desirudin group (4.5 percent) than in the enoxaparin group (7.5 percent), for a relative reduction in risk of roughly 40 percent. This finding is consistent with the results of two previous multicenter trials, in which the antithrombotic efficacy of desirudin was compared with that of unfractionated heparin in patients undergoing elective hip surgery.[4,5]

Patients undergoing orthopedic surgery are considered to be at high risk for thromboembolic complications, and the efficacy of prophylaxis is well documented.[15-18] In elective hip surgery, low-molecular-weight heparin, adjusted-dose unfractionated heparin, and adjusted-dose warfarin are the recommended methods.[16] The incidence of deep-vein thrombosis after total hip or knee replacement has been shown to be as high as 21 to 55 percent, however, despite the use of low-molecular-weight heparin or adjusted-dose warfarin as prophylaxis.[19] It is of vital importance to reduce the risk of thromboembolism further in this high-risk population. Considering the feasibility and safety of an antithrombotic regimen, a fixed dose is preferable to regimens that require cumbersome laboratory monitoring and adjustment of doses.

The difference in the timing of the first dose of the study drugs in this trial may have affected the results. Since desirudin has a shorter half-life than enoxaparin, desirudin was given immediately before surgery and two times daily thereafter. The superior benefit of desirudin may have resulted in part from the fact that it was administered just before surgery. A more efficient mode of action of this specific inhibitor of thrombin may also have accounted for its superiority to heparin, as demonstrated in this and two other large multicenter trials.[4,5] Another advantage of desirudin is that it is not associated with immune-mediated thrombocytopenia, which can occur with heparin preparations. In our trial there were no reported cases of thrombocytopenia in either treatment group.

The efficacy analysis was based on the outcome during the treatment period and did not include events during the follow-up period, when the majority of patients had been discharged from the hospital. The data generated during the follow-up period should be interpreted with caution, since concomitant medications were not all recorded and screening for thromboembolic events was not performed systematically during this period.

The proportion of patients with adequate venograms was high (86 percent of those who underwent venography). For a venogram to be evaluated, all veins had to be visualized. The high rate of venograms that could be evaluated in this study is a result of a thorough educational program, in which all radiologists in the trial had to participate. A compara-

ble high-quality trial has reported a similar rate of adequate venograms.[19]

The results of venographic screening are a surrogate end point for symptomatic deep-vein thrombosis and potential pulmonary embolism. Clinical data from meta-analyses of multiple trials show a reduction in asymptomatic deep-vein thrombosis and fatal pulmonary embolism with the use of antithrombotic agents.[20] Autopsy data also show a strong correlation between proximal deep-vein thrombosis and pulmonary emboli.[21] Clinical trials using mandatory venography and lung scanning corroborate these results, showing an increased risk of pulmonary embolism in patients with proximal deep-vein thrombosis and a lower risk when the thrombi are restricted to the calf region.[22,23] Thus, the reduction in the risk of major thromboembolic events among the patients treated with desirudin in this study, as compared with those who received enoxaparin, has important clinical implications.

In conclusion, the results of this study confirm the hypothesis that specific inhibition of thrombin is effective in preventing postoperative thromboembolism in high-risk patients who have undergone hip-replacement surgery. The patients who received desirudin twice daily for at least eight days had a 40 percent lower risk of proximal deep-vein thrombosis than those given enoxaparin, a low-molecular-weight heparin. The treatment regimens were equally safe and did not require specific laboratory monitoring.

Supported by Novartis.

APPENDIX

The principal investigators in this study were as follows: Austria — H. Jakubek, A.Ö. Krankenhaus der Barmherzigen Schwestern, Linz; H. Niessner, A.Ö. Krankenhaus, Wiener Neustadt; Belgium — T. Pittevils, St. Jansziekenhuis, Ghent; L. van den Daelen, Stedelijk Ziekenhuis OCMW, Roeselare; J. van Overschelde, Aalsters Stedelijk Ziekenhuis, Aalst; Denmark — S. Solgaard, Hillerød Sygehus, Hillerød; C. Tørholm, KAS Gentofte, Hellerup; P. Wille-Jørgensen, Bispebjerg Hospital, Copenhagen; U. Lucht, Aarhus; France — B. Tomeno, Hôpital Cochin, Paris; C. Mazel, CMC Porte de Choisy, Paris; P. Mamoudy, Hôpital de la Croix Saint-Simon, Paris; M. Fouche, Rennes Polyclinique Sévigné, Cesson-Sévigné; Germany — P. Mouret, Städtische Kliniken Höchst, Frankfurt–Höchst; H.U. Paul, Hellmuth-Ulrici-Kliniken, Sommerfeld; Italy — A. Corradi and R. Ghezzi, Ospedale Gaetano Pini, Milan; L. Tessari and F. Ravasi, Ospedale S. Raffaele, Milan; G. Massè and P.P. Mauro, Ospedale Santissima Annunziata, Savigliano; the Netherlands — D.M. Paré, Streekziekenhuis Midden-Twente, Hengelo; H.T.F. van de Weijer, Lorentz Ziekenhuis, Zeist; G.H.I.M. Walenkamp, Academisch Ziekenhuis, Maastricht; Spain — L.P. Garces, Hospital Clinic I Provinicial, Barcelona; E. Castellet-Feliu, Hospital Vall Hebrón, Barcelona; Sweden — B. Eriksson, Sahlgrenska Universitetssjukhuset–Östra, Göteborg; L. Ahnfelt, NÄL Hospital, Trollhättan; R. Berg, Höglandssjukhuset, Eksjö; J. Soreff, Södersjukhuset, Stockholm; Switzerland — A. Burckhardt, Kantonsspital, Olten; B. Noesberger, Regionspital, Interlaken; P. Engelhardt, Kantonsspital, St. Gallen; B. Gerber, Hôpital Pourtalès, Neuchâtel.

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